Methods in Metal-Mediated Hydroamination and Their Applications in Total Synthesis

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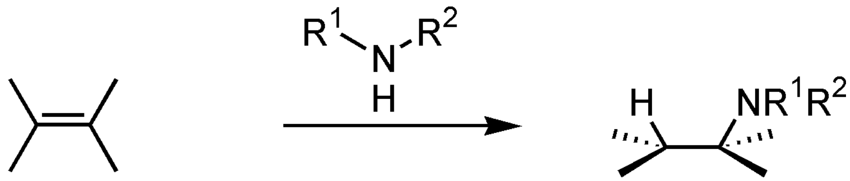
2 February 2006
University of California, Berkeley

Egypt, The Nineteenth Century, and the Inspiration for Hydroamination

Amun



Suffers from:

- Electrostatic repulsion
- Concerted [2+2] Symmetry Forbidden
- Large Orbital Energy Difference
- Heating shifts Equlibrium to the left because of $-\Delta S$

Charles Adolphe Wurtz

Metal-Catalyzed Hydroamination

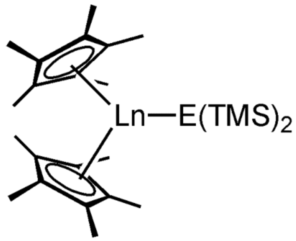
- Catalysis by Lanthanides and Actinides
  - Intramolecular Examples
  - Intermolecular Examples
  - Asymmetric Examples
  - Use in Total Synthesis

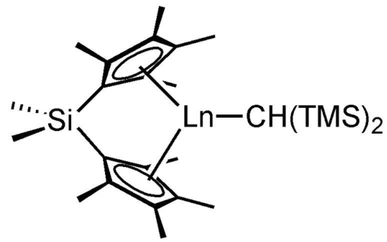
- Catalysis by Early Transition Metals
  - Intramolecular Examples
  - Intermolecular Examples
  - Use in Total Synthesis

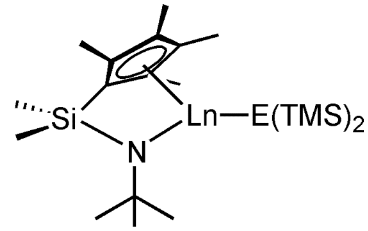
- Catalysis by Late Transition Metals
  - Intermolecular Examples
  - Intramolecular Examples
  - Asymmetric Examples

Organolanthanide Catalysts for Hydroamination

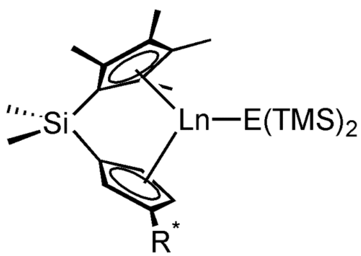
Achiral Catalysts

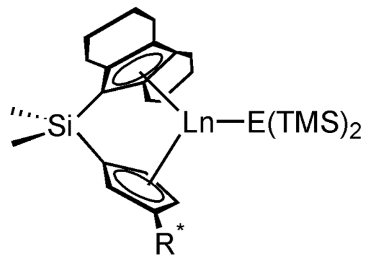


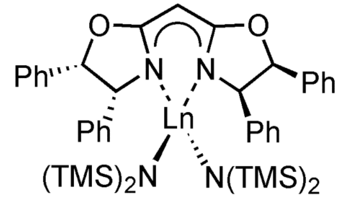




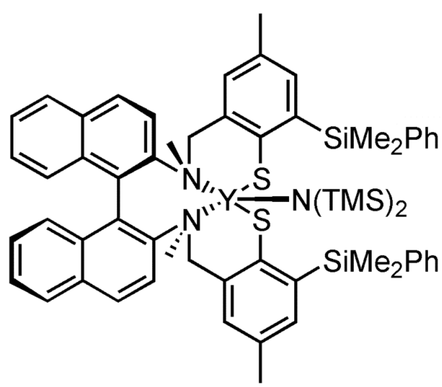
Chiral Catalysts

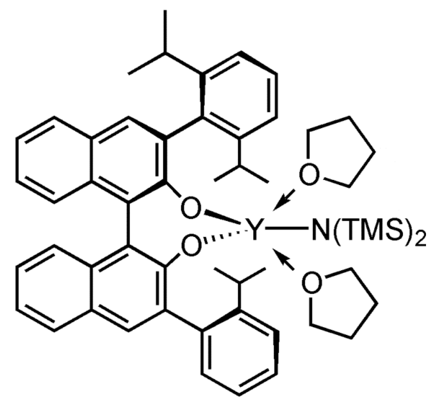






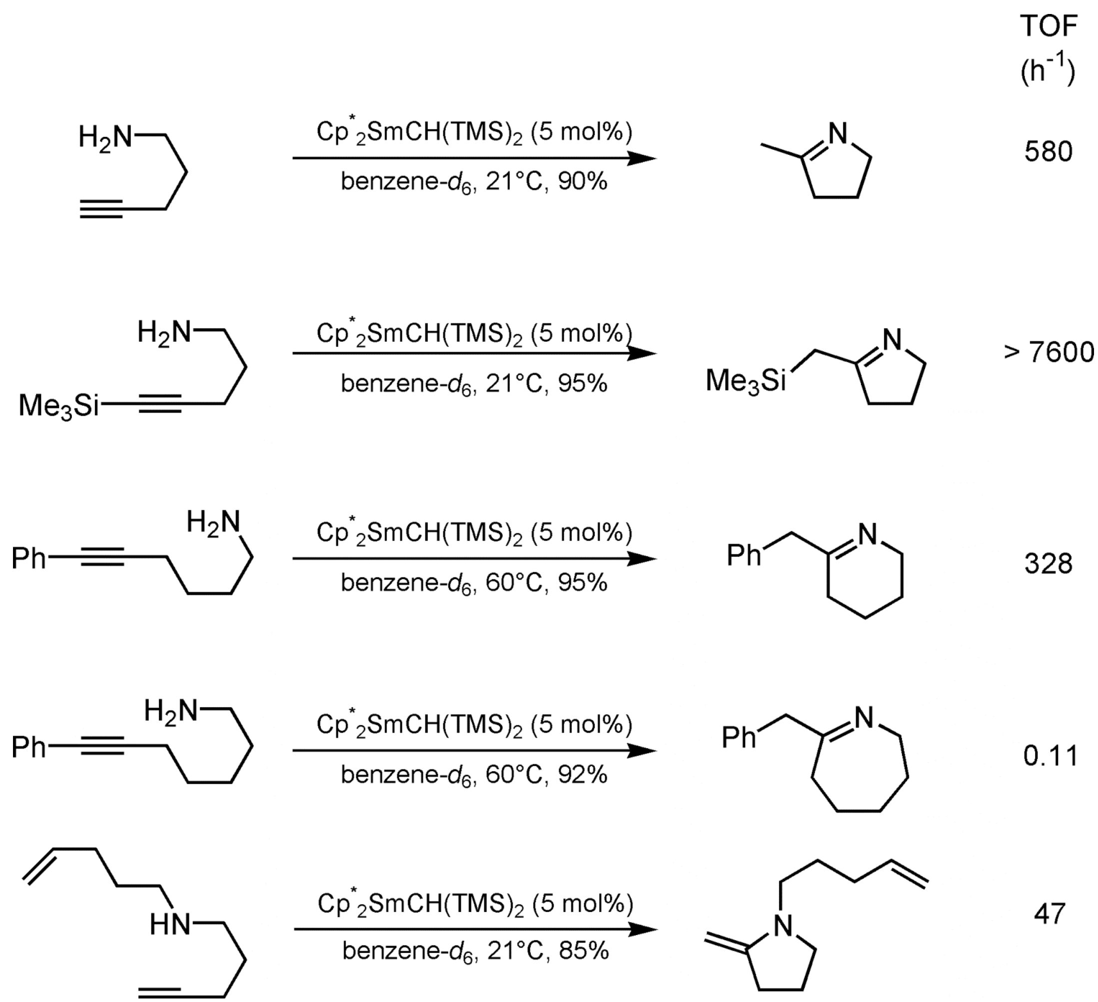
Ln = La, Nd, Sm, Y, Lu
E = N, CH
R* = (–)-menthyl,
(+)-neomenthyl,
and (–)-phenylmenthyl





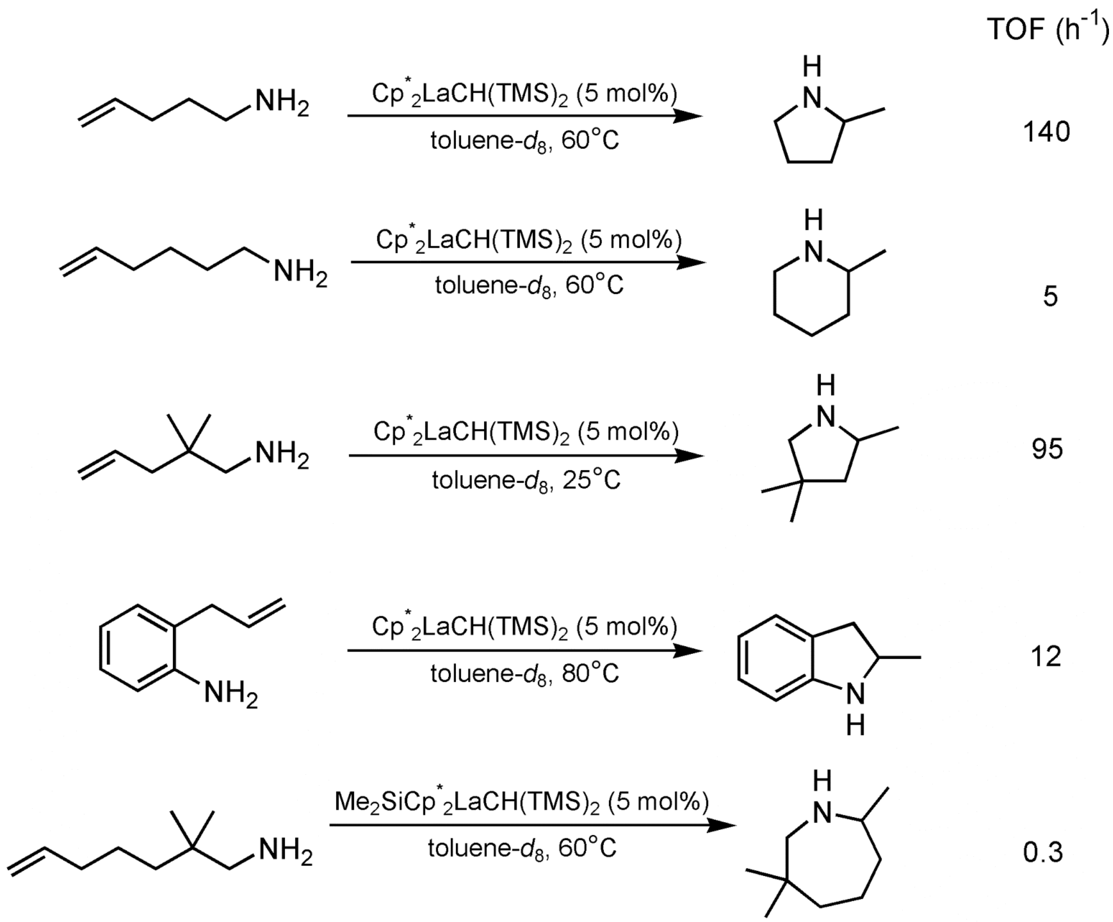
Marks, T.J. et al. *Acc. Chem. Res.* **2004,** *37*, 673.

Intramolecular Hydroamination of Aminoalkenes



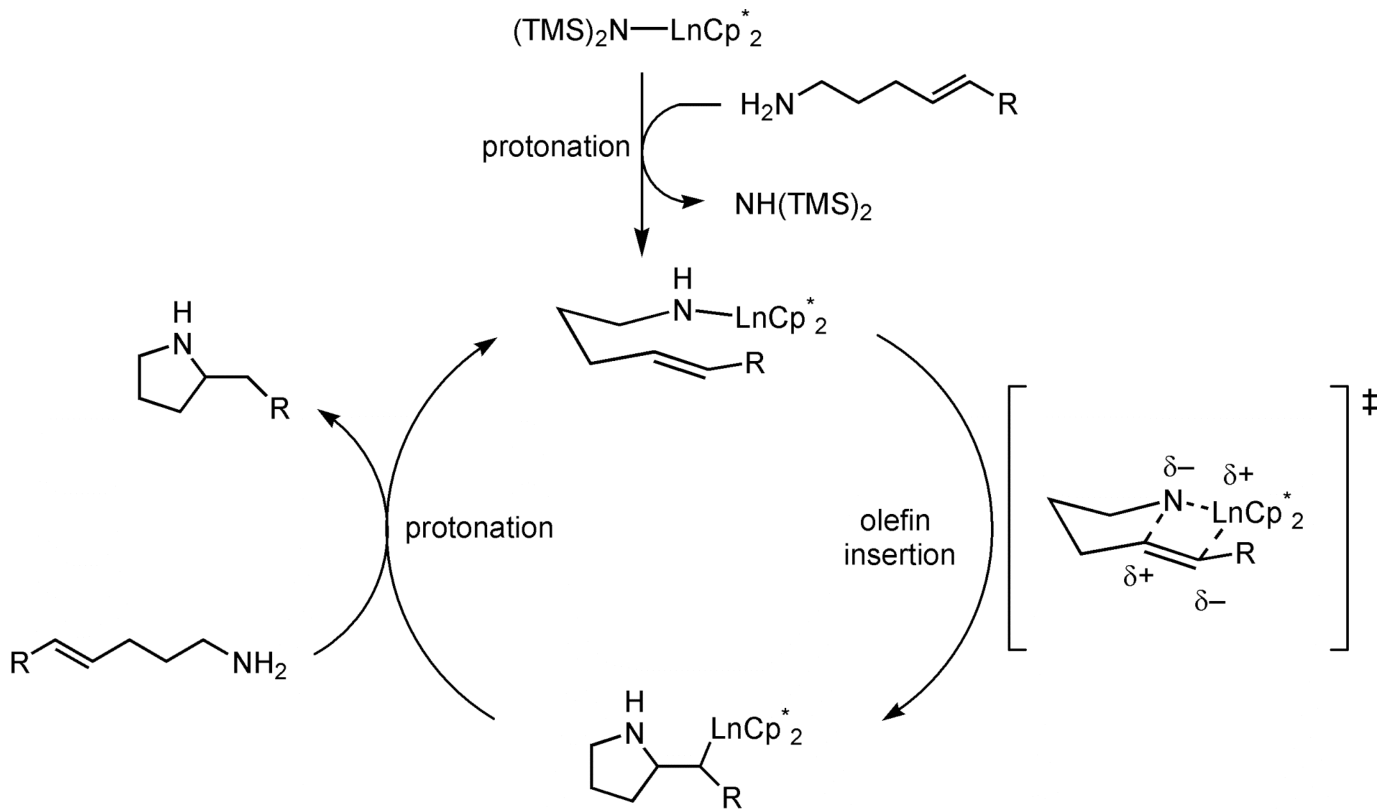
Marks, T. J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9295.

Intramolecular Hydroamination of Alkenes



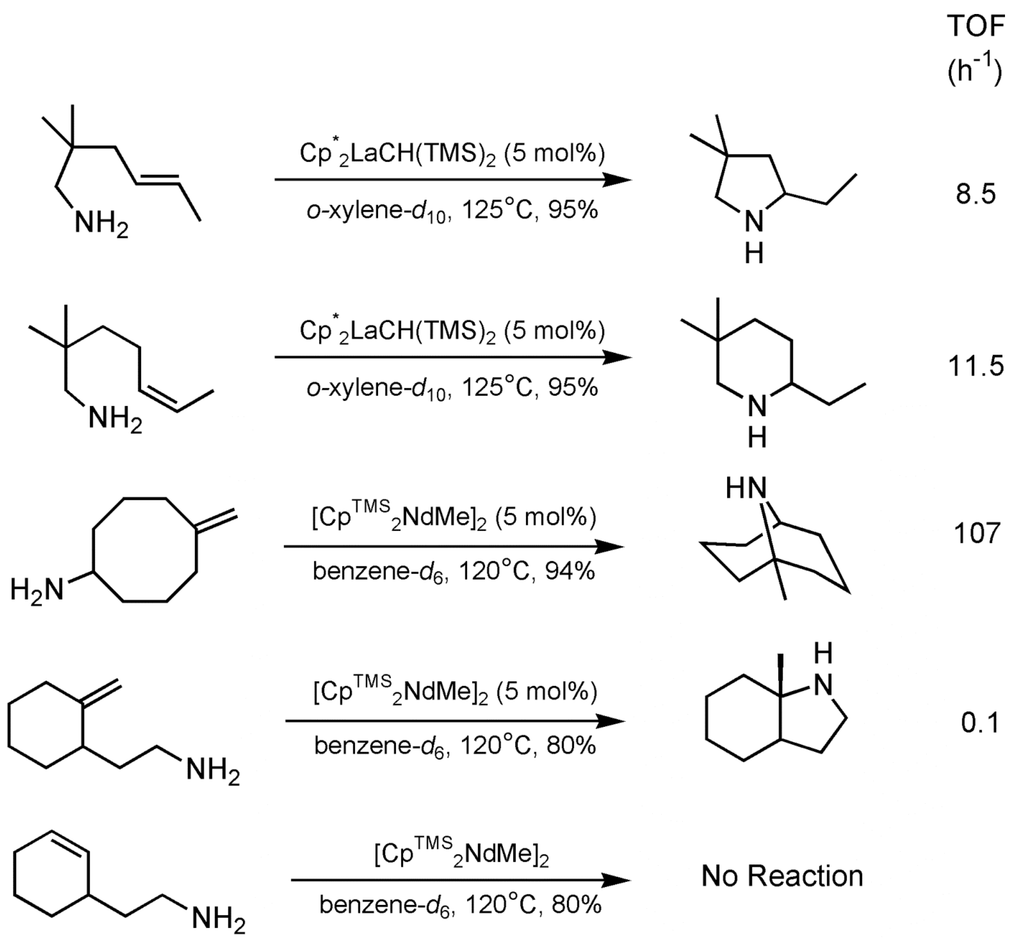
Marks, T.J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9295.
Marks, T.J. et al. *Organometallics*, **1994**, *13*, 439.

Mechanism of Organolanthanide Hydroamination



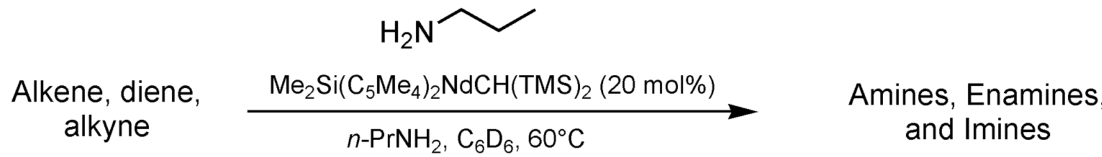
Marks, T.J.et al. *J. Am. Chem. Soc.* **1992**, *114*, 275.

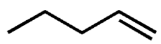
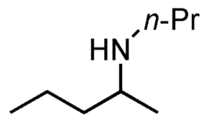
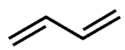
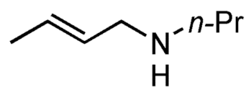
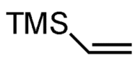
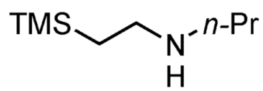
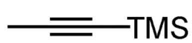
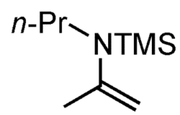
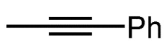
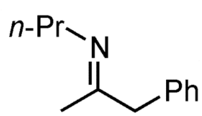
Steric Hinderance in the Hydroamination of Alkenes



Marks, T. J. et al. *J. Am. Chem. Soc.* **1998**, *120*, 1757.
Marks, T. J. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9295.
Molander, G.A. et al. *J. Org. Chem.* **1998,** *63*, 8983.

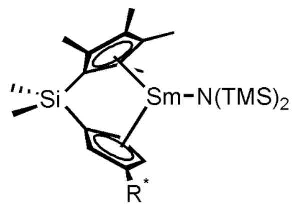
Intermolecular Hydroamination of Alkenes

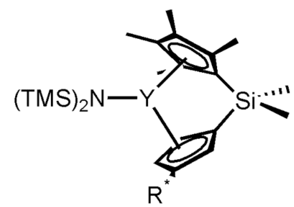


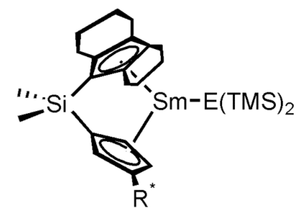
Substrate	Product	TOF (h^{-1})	Yield (%)
		0.4	90
		0.3	90
		2	93
		13	62 (isolated)
		2	85

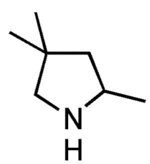
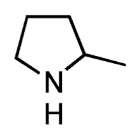
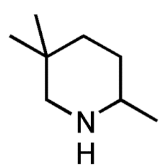
Marks, T.J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

Asymmetric Hydroamination with Chiral Lanthanocenes



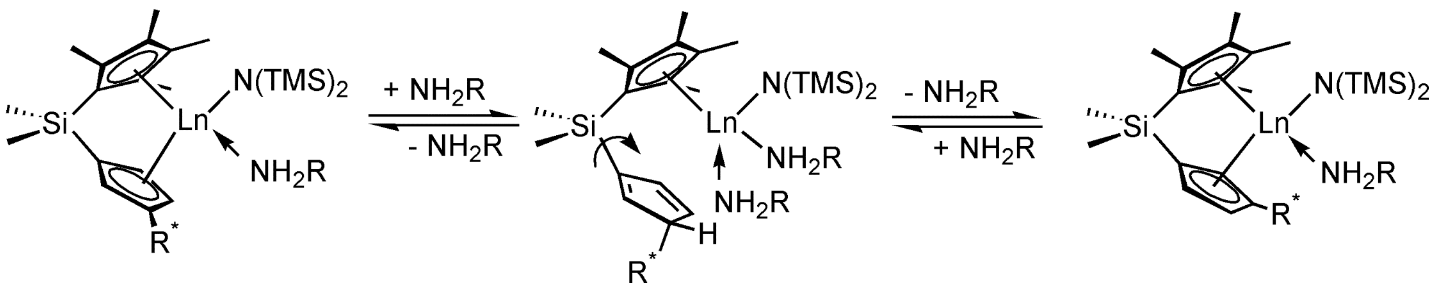




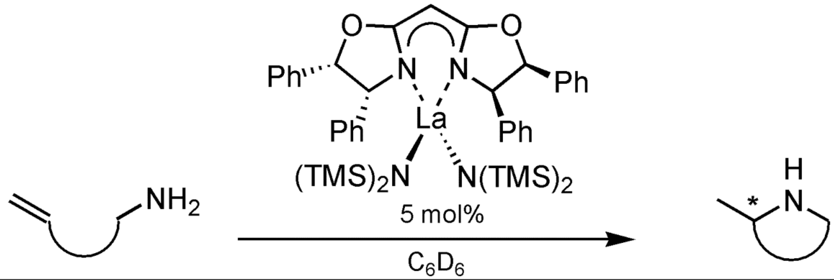
	(S)-(–)-menthylCpSm	**1:** (*R*)-(–)-phenylmenthylCpY **2:** (*R*)-(–)-menthylCpY **3:** (*R*)-(+)-neomenthylCpY	**1:** (S)-OHF(–)-menthylCpSm **2:** (S)-OHF(–)-menthylCpY
	-30°C, 74% ee (*S*) config.	**1**, 25°C, 56% ee (*S*) config.	**1**, 25°C, 32% ee (*S*) config.
	-0°C, 72% ee (*S*) config.	**2**, 25°C, 69% ee (*S*) config.	**1**, 25°C, 46% ee (*S*) config.
	25°C, 15% ee (*R*) config.	**3**, 25°C, 17% ee (*R*) config.	**2**, 25°C, 67% ee (*S*) config.

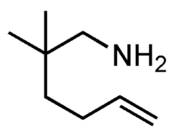
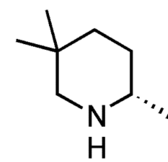
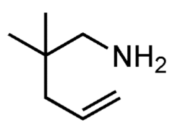
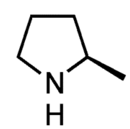
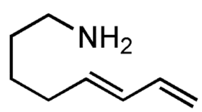
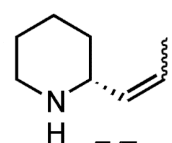
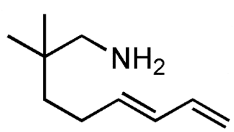
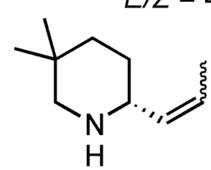
Marks, T.J. et al. *J. Am. Chem. Soc.* **1994**, *116*, 10212.
Marks, T.J. et al. *J. Am. Chem. Soc.* **1994**, *116*, 10241.

Epimerization of Chiral Lanthanocenes



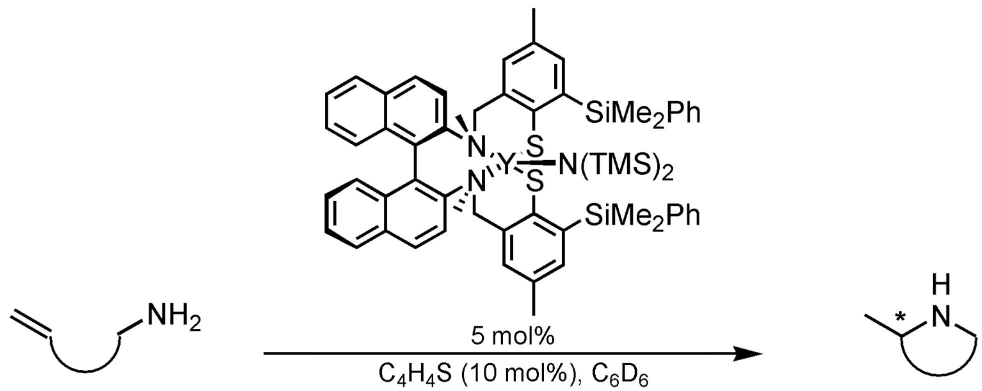
Bisoxazolines in Asymmetric Hydroamination

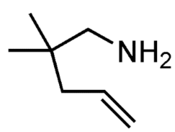
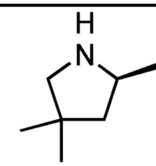
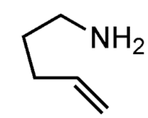
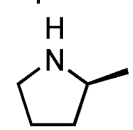
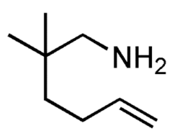
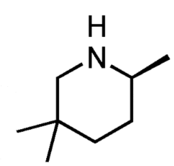
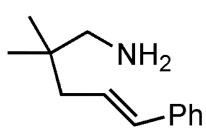
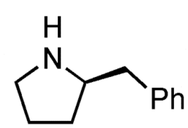


Substrate	Temperature (°C)	TOF (h^{-1})	Product	%ee
	60	4.0		56
	23	25		40
	60	0.6	 *E/Z* = 41:59	54
	23	1.4	 *E/Z* = 39:57	45

Marks, T.J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

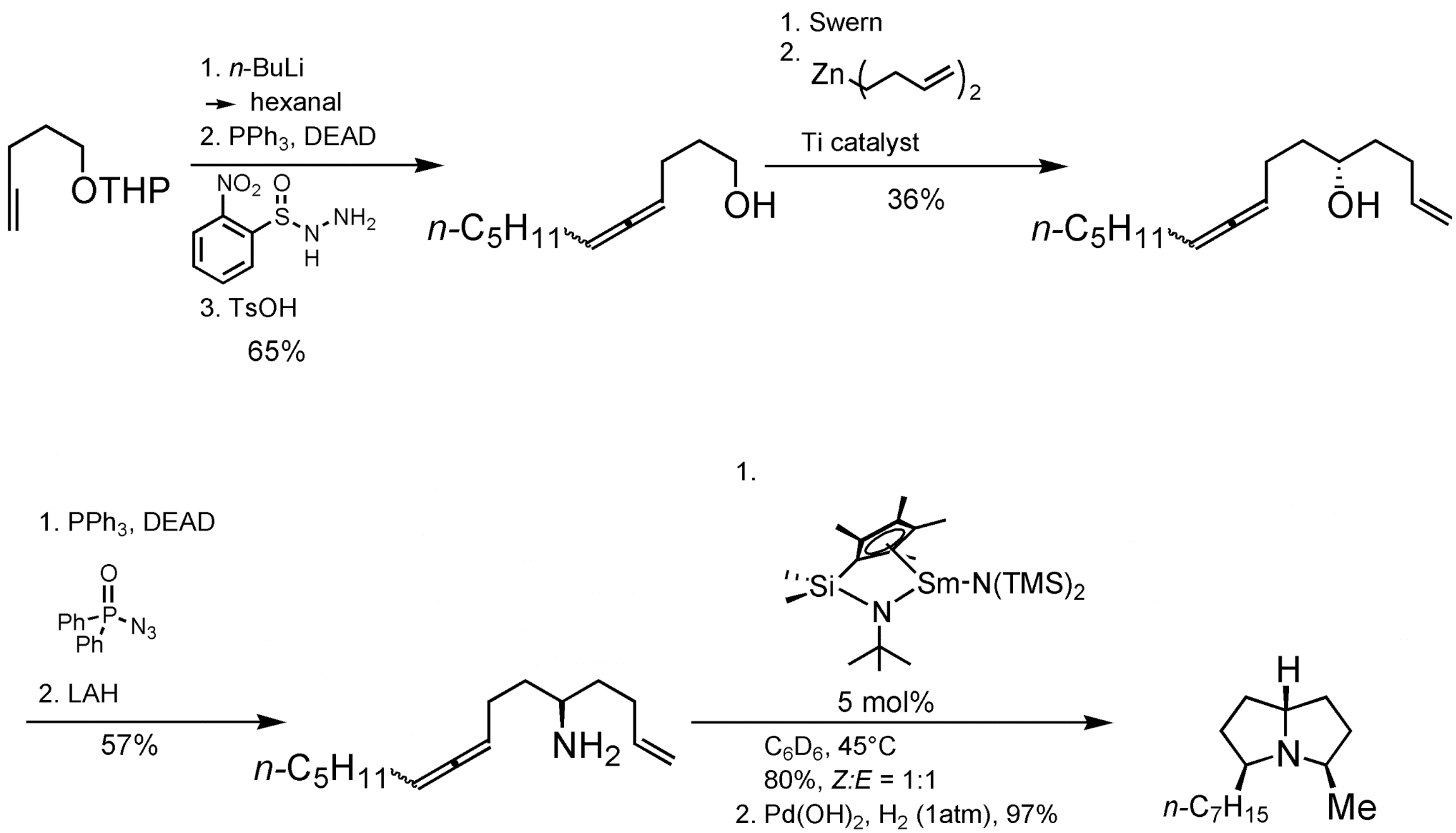
AHA with Chiral Yttrium Bis-Thiolate Complexes



Substrate	Temperature (°C)	Time (h)	Product	%ee
	60	9		87
	60	8		81
	75	3		80
	60	3		82

Livinghouse, T. et al. *Org. Lett.* **2005**, *7*, 1737.

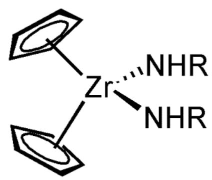
Total Synthesis of (+)-Xenovenine

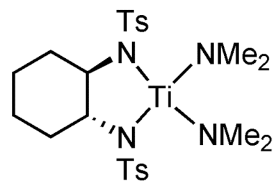


Marks, T.J. et al. *J. Am. Chem. Soc.* **1999**, *121*, 3633-3639.

Group 4 Catalysts for Hydroamination

Bergman

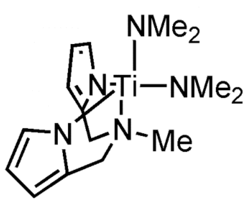


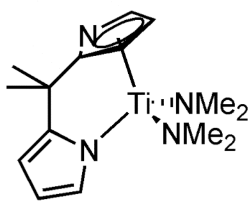


Livinghouse

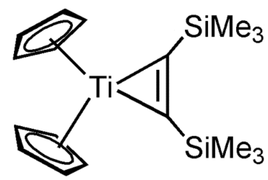
$CpTiCl_3$

Odom

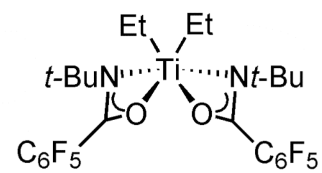




Beller

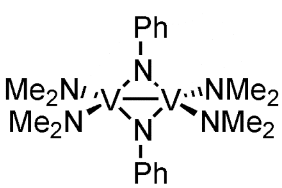


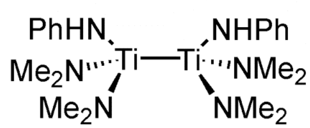
Schafer



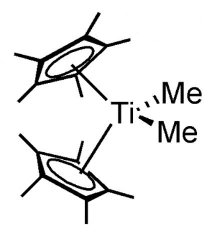
$Ti(NMe_2)_4$

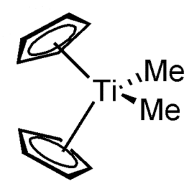
Lorber

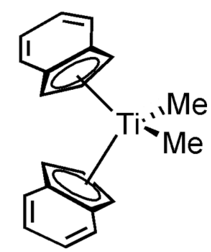




Doye

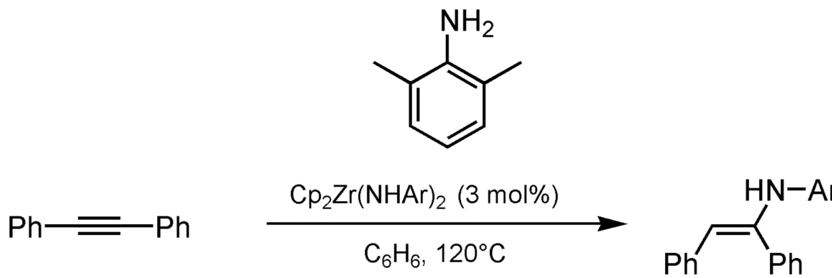




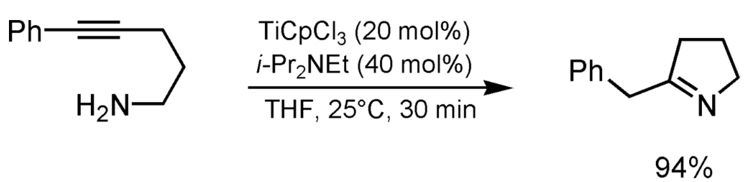


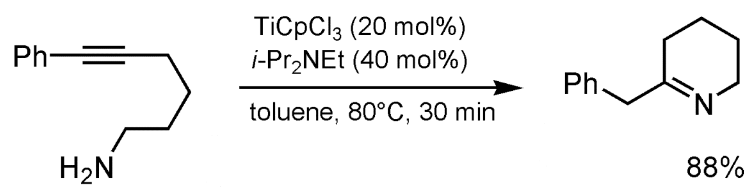
Doye et al. *Eur. J. Org. Chem.* **2003**, 935.

Seminal Papers in the Development of Group IV Hydroamination



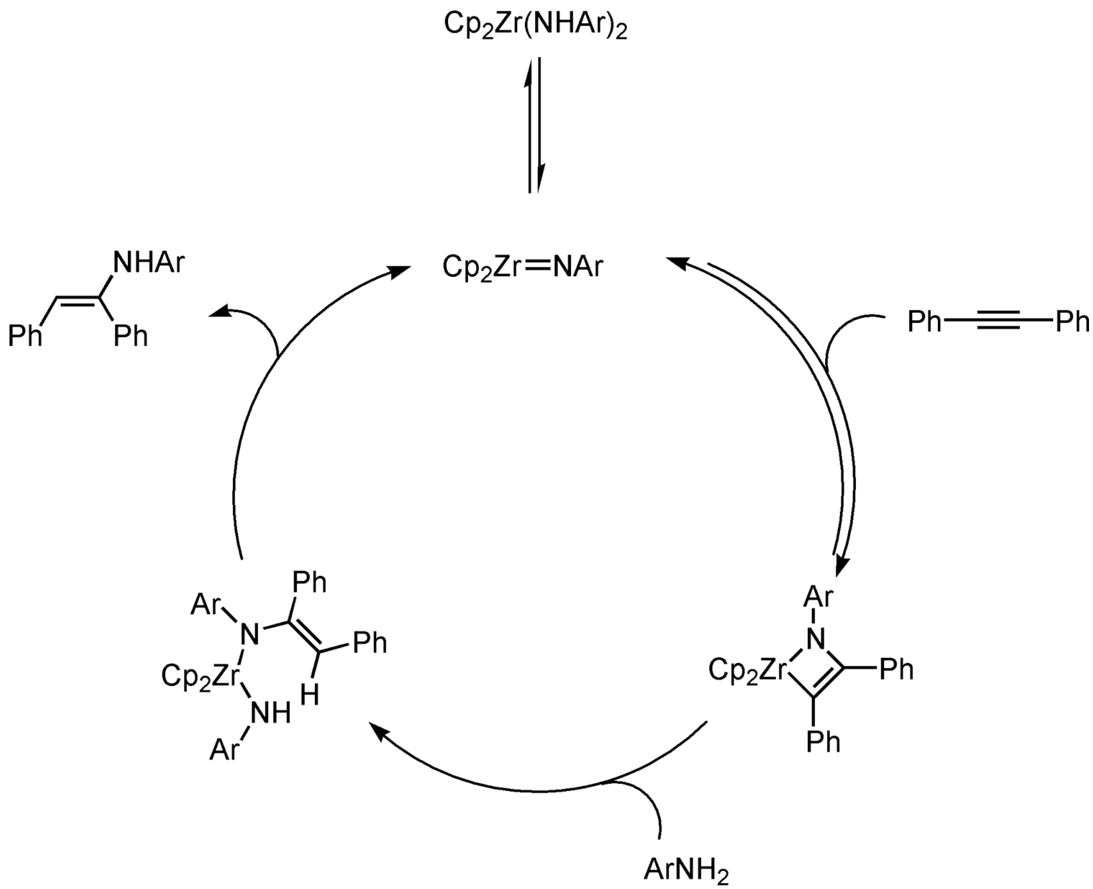
Bergman, R.G. et al. *J. Am. Chem. Soc.* **1992**, *114*, 1708.





Livinghouse, T. et al. *J. Am. Chem. Soc.* **1992**, *114*, 5459.

The Bergman Mechanism for Group IV Hydroamination

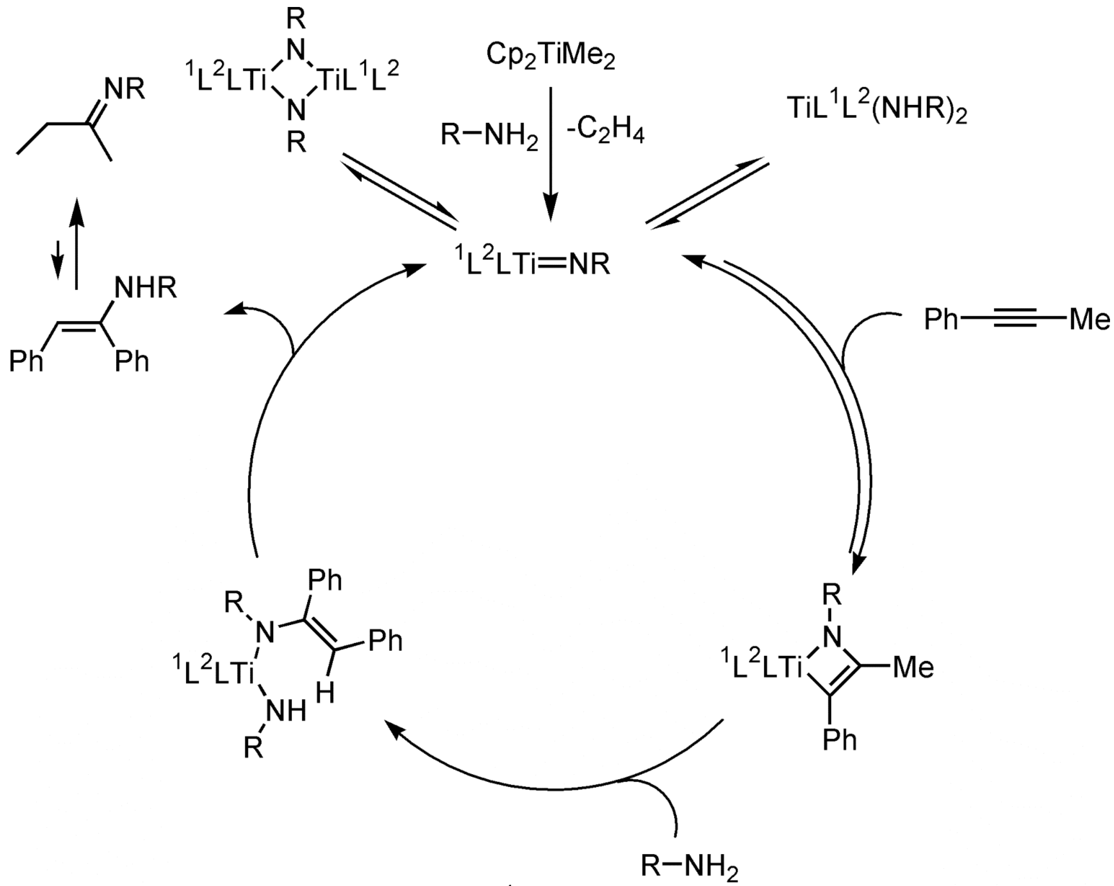


Ar = 2,6-dimethylphenyl

Only Works with Sterically Hindered Amines

Bergman, R.G. et al. *J. Am. Chem. Soc.* **1992**, *114*, 1708.

Mechanism for Hydroaminations with Ti Catalysts



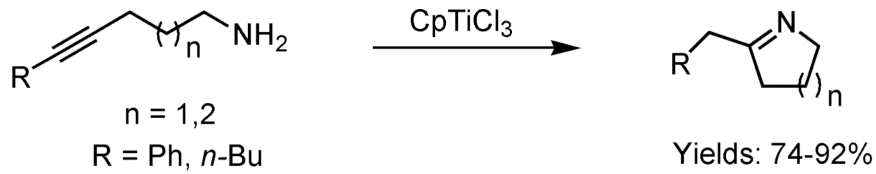
^1L = Cp

^2L = NHR

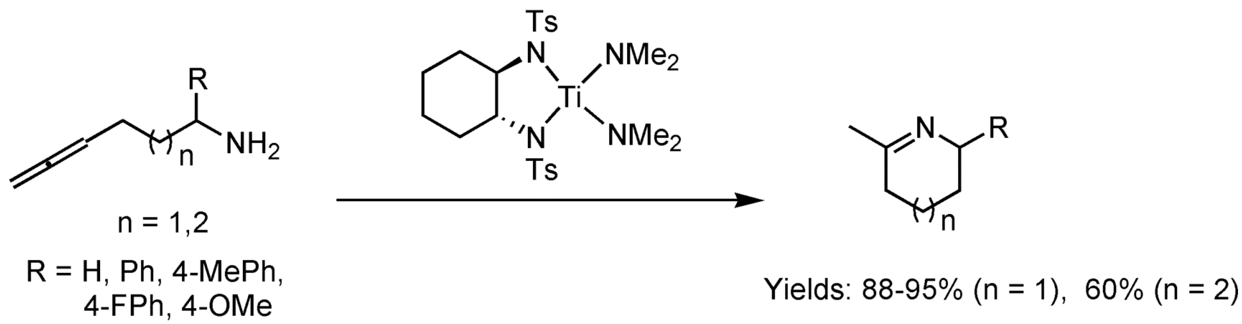
R = 4-MeC_6H_4

Doye, S. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2305.

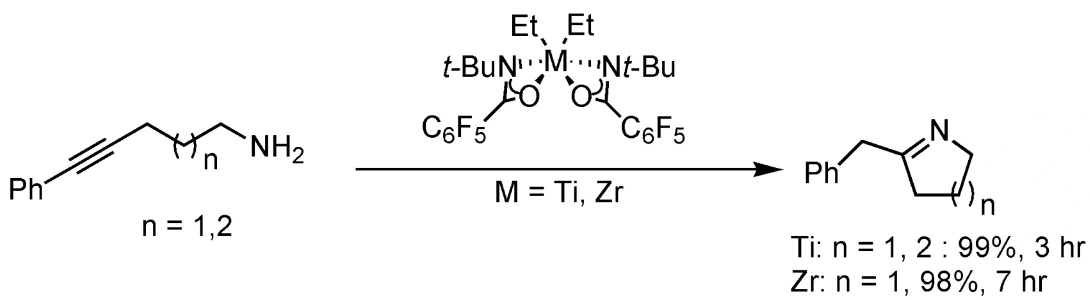
Intermolecular Allene and Alkyne Hydroaminations with Ti Catalysts



Livinghouse et al. *J. Am. Chem. Soc.* **1992**, *114*, 5459.

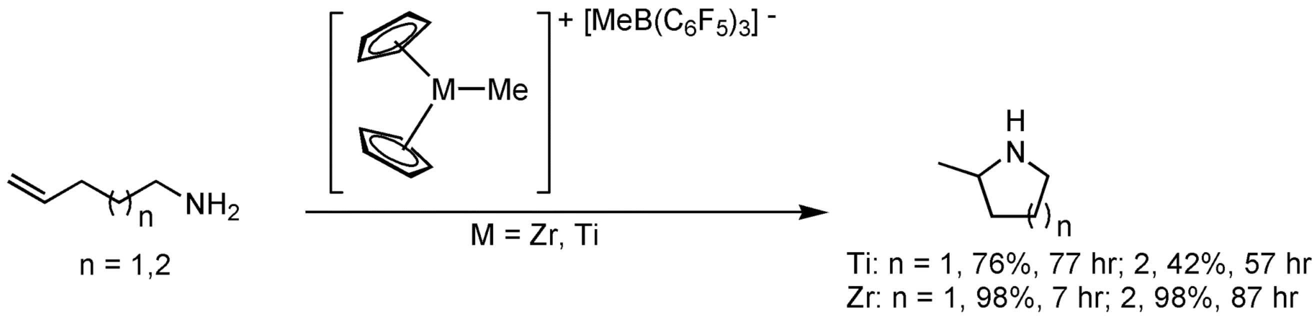


Bergman et al. *J. Am. Chem. Soc.* **2003**, *125*, 11956.

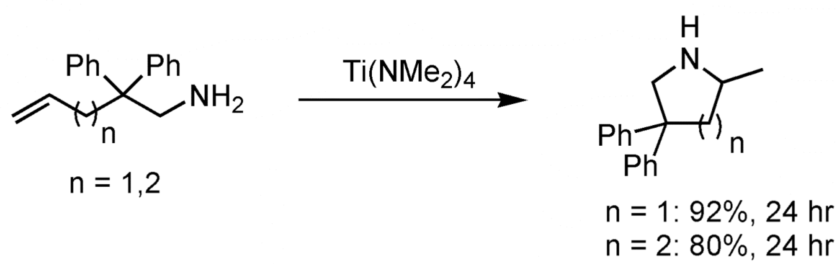


Schafer et al. *Chem. Commun.* **2003**, 2462.

Intermolecular Olefin Hydroaminations with Ti Catalysts

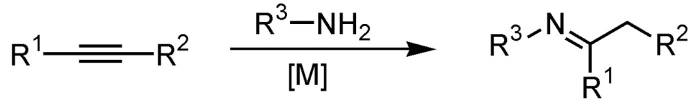


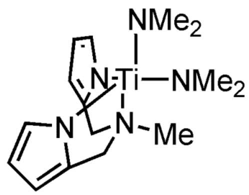
Hultzsch et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 5542.



Schafer et al. *Org. Lett.* **2005**, *7*, 1959.

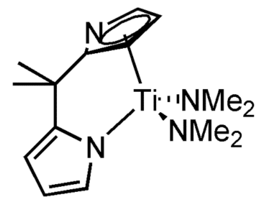
Markovnikov Selective Hydroamination Catalysts





R^1 = Ph, *n*-Bu
R^2 = H
R^3 = Ph
Time = 2-8 hr
Yield = 26-90%
M: Anti-M = up to 50:1

Odom et al.
Organometallics **2001**, *20*, 5011.



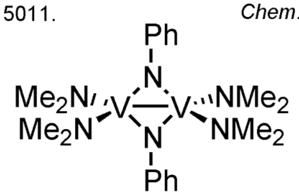
R^1 = Ph, *n*-Bu
R^2 = H
R^3 = Ph
Time = 5 min
Yield = 41-57%
M: Anti-M = up to 40:1

Odom et al.
Chem. Commun. **2003**, 586.

$Ti(NMe_2)_4$

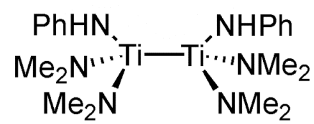
R^1 = Ph, *n*-Bu
R^2 = H
R^3 = Ph, *t*-Bu
Time = 2-10 hr
Yield = 16-90%
M: Anti-M = up to 100:1

Odom et al.
Organometallics **2001**, *20*, 3967



R^1 = Ph, *n*-Bu
R^2 = H, Me
R^3 = Ph
Time = 20 hr
Yield = 41-85%
M: Anti-M = up to 100:1

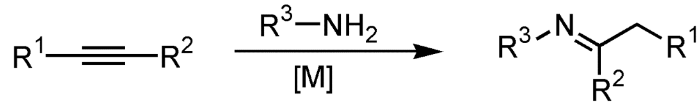
Lorber et al.
Organometallics **2004**, *23*, 1845.

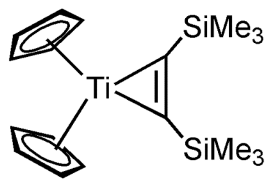


R^1 = Ph, *n*-Bu
R^2 = H, Me
R^3 = Ph, *t*-Bu
Time = 2 hr
Yield = 85-94%
M: Anti-M = up to 100:1

Lorber et al.
Organometallics **2004**, *23*, 1845.

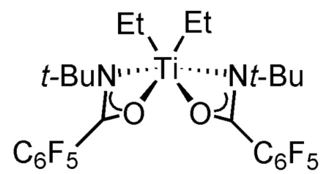
Anti-Markovnikov Selective Catalysts for Hydroamination





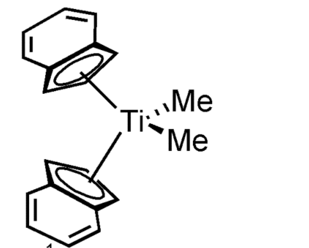
R^1 = Ph, *n*-Bu, *n*-Pent, *n*-hex
R^2 = H
R^3 = *t*-Bu
Time = 2-8 hr
Yield = 26-90%
Anti-M : M = 63:1 to 99:1

Beller et al.
Angew. Chem. Int. Ed. **2002**, *41*, 2541.



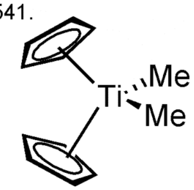
R^1 = *n*-Bu
R^2 = H
R^3 = *t*-Bu, *i*-Pr, CH_2Ph
Time = 15 min
Yield = 50-93%
Anti-M : M = 12:1 to 99:1

Schafer et al.
Chem. Commun. **2003**, 2462.



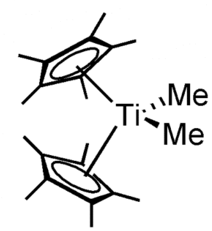
R^1 = *n*-hex, 4-OMePh
R^2 = H, Me
R^3 = CH_3Ph, *t*-Bu
Time = 1-8 hr
Yield = 77-99%
Anti-M : M = 1.5:1 to 99:1

Doye et al.
Chem. Eur. J. **2004**, *10*, 3059.



R^1 = Ph
R^2 = Me, Et, *n*-Prop
R^3 = *t*-Bu, Ph, aniline deriv.
Time = 24 hr
Yield = 57-99%
Anti-M : M = 99:1 in all cases

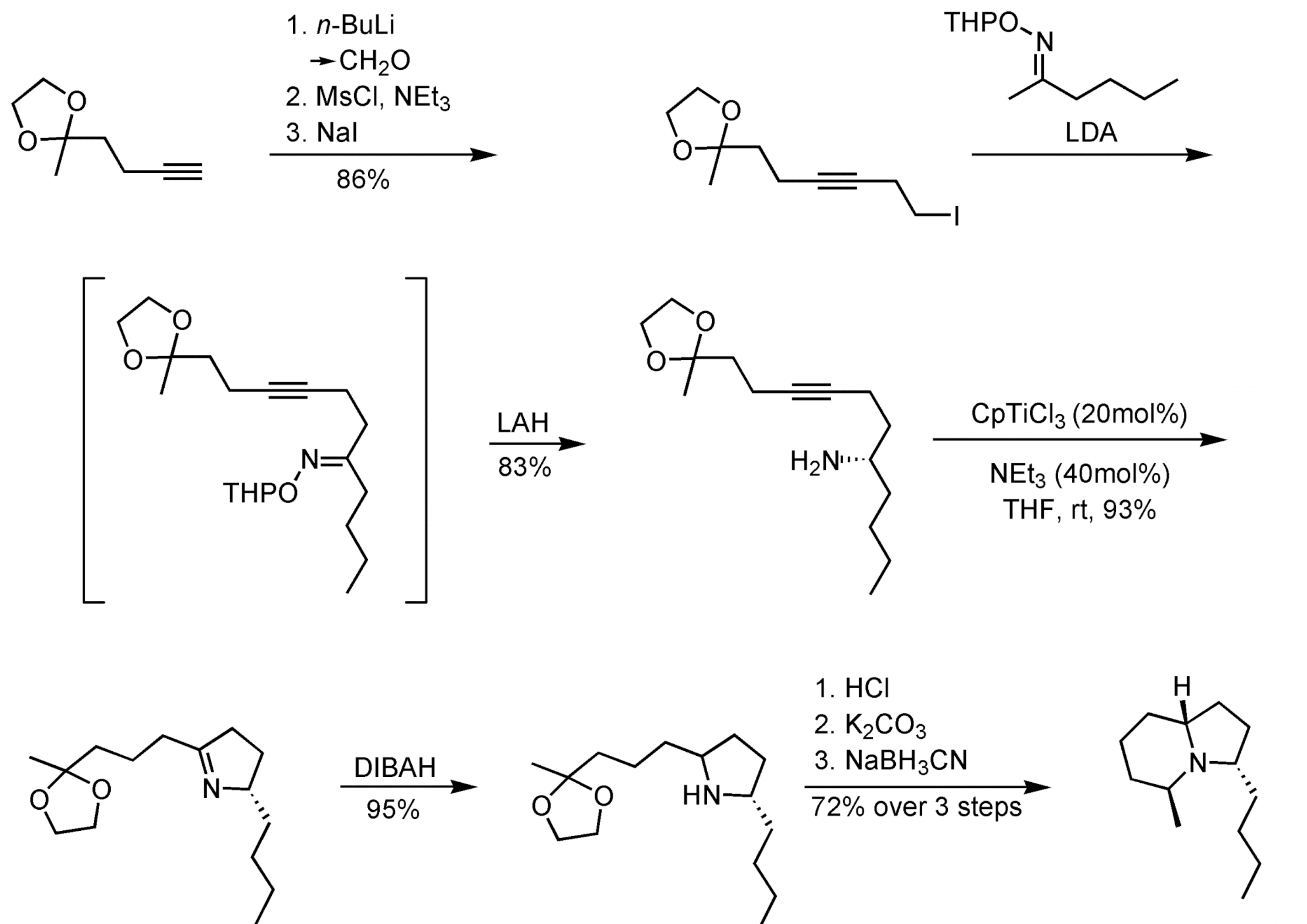
Doye et al.
Angew. Chem. Int. Ed. **2005**, *44*, 2951.



R^1 = Ph
R^2 = Me
R^3 = *n*-Bu, CH_2Ph
Time = 24 hr
Yield = 95%
Anti-M : M = 1.2:1 to 31:1

Doye et al.
J. Org. Chem. **2002**, *44*, 1961.

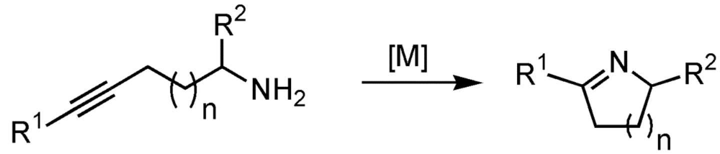
The Livinghouse Synthesis of (±)-Monomorine



(±)-monomorine

Livinghouse et al. *J. Org. Chem.* **1992**, *57*, 1324.

Late-Metal Catalyzed Aminoalkyne Hydroamination



n = 2

R^1 = n-C_5H_{11}, n-C_6H_{13}

R^2 = H, Me

M = $PdCl_2(CH_3CN)_2$

Yields = 100%

Utimoto et al. *Heterocycles* **1987**, *30*, 297.

n = 1, 2

R^1 = n-Bu, Ph, H

R^2 = H, CH_3, n-C_8H_{17}

M = $PdCl_2(CH_3CN)_2$

10 examples

Yields = 65-71%

Utimoto et al. *J. Org. Chem.* **1991**, *56*, 5812.

n = 2

R^1 = R^2 = H

M = $K[Co(CO)_3(PPh_3)]$, 66%

$[Ir(COD)(PCy_3)(py)]PF_6$, 76%

$[Pd(dppf)][NO_3]_2 \cdot CH_2Cl_2$, 77%

$[Pd(CH_3CN)_2][BF_6]_2$, 67%

$[Cu(CH_3CN)_4]PF_6$, 93%

$[Ag(Triphos)]BF_4$, 75%

$AuCl_3$, 71%

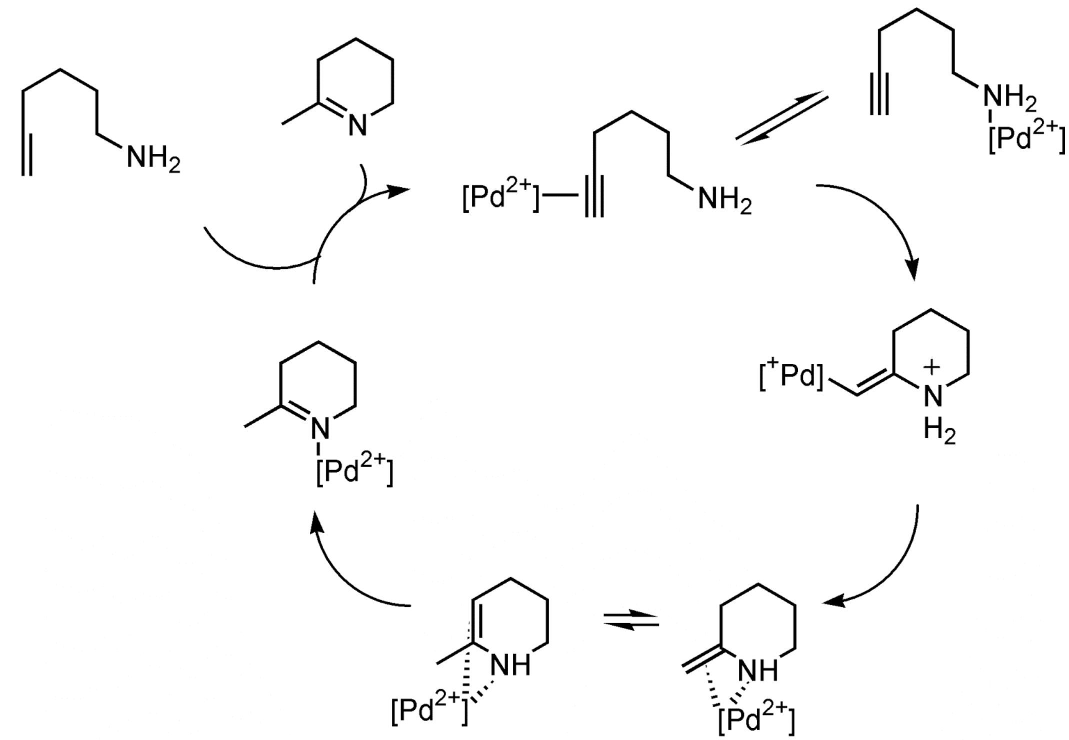
$Zn(O_3SCF_3)_2$, 85%

$Cd(NO_3)_2 \cdot 4H_2O$, 98%

$Hg(NO_3)_2 \cdot H_2O$, 80%

Müller et al. *J. Chem. Soc., Dalton Trans.* **1998**, 583.

Mechanism for Intramolecular Hydroamination with Pd Catalysis



Müller et al. *J. Chem. Soc., Dalton Trans.* **1998**, 583.

Importantly depends on oxidation state of the metals… only d_8 and d_{10} participate!

Hartwig's Colorimetric Assays to Assess Activity in the Hydroamination of Aniline

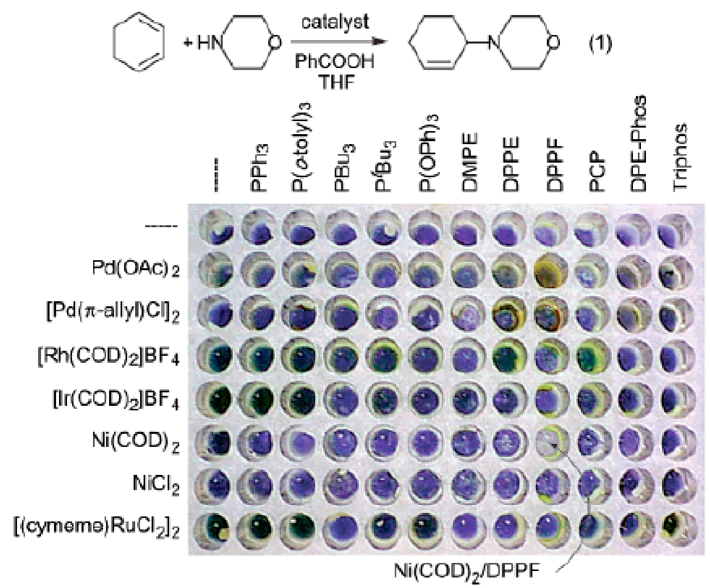
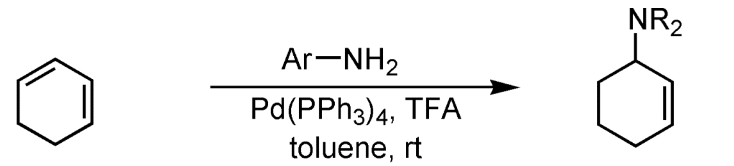


Figure 1. Evaluation of catalysts for eq 1, visualized by the combination of acetaldehyde, sodium nitroferricyanide(III) dihydrate ($Na_2Fe(CN)_5NO\cdot 2H_2O$), and NaOH. DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

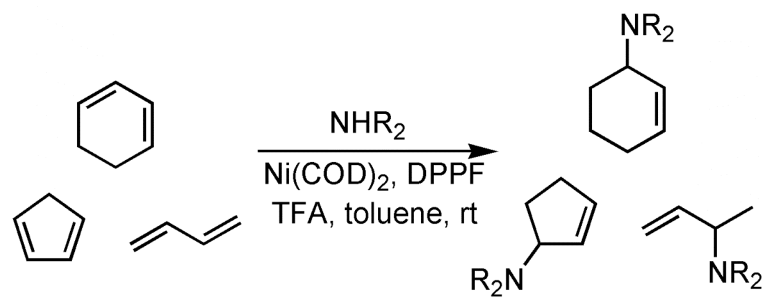


16 examples,
78-99%

Ar = Phenyl, naphthyl, pyridnyl
also with subst on Ar where
R = Me, CF_3, CO_2Et, OMe, Br

Assay involves addition of furfural

Hartwig et al. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

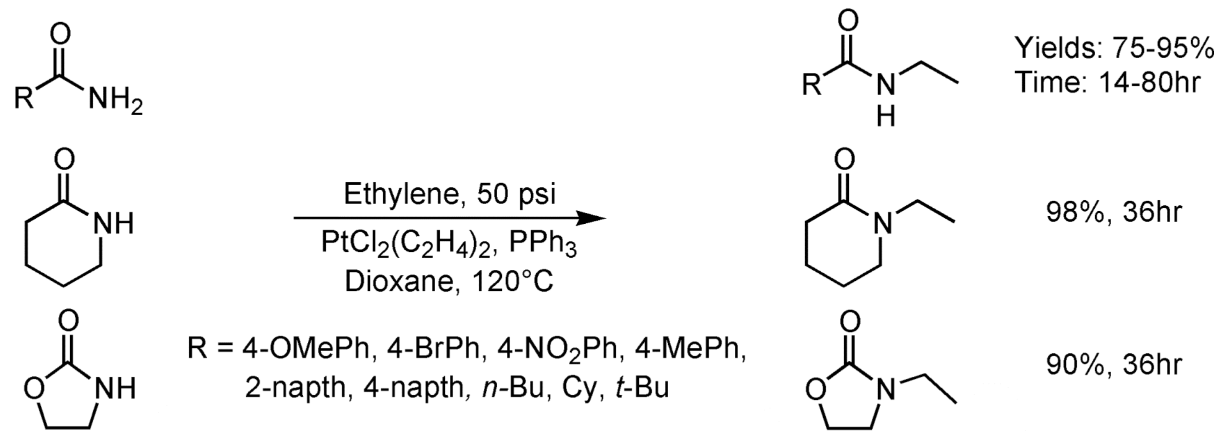


16 examples, 56-94%
0.5-113hr

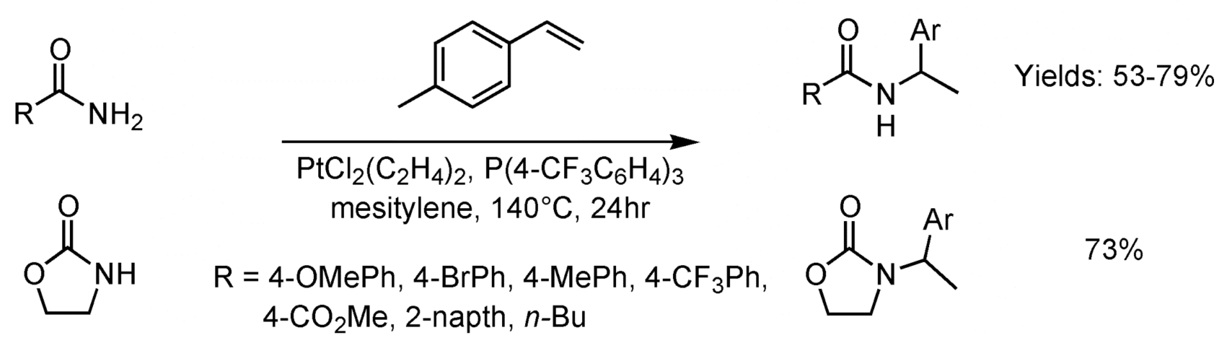
R = H, Me, Et, Bu, Cy, Bn,
also with piperidine and morpholine

Hartwig et al. *J. Am. Chem. Soc.* **2002**, *124*, 3669.

Widenhoefer's Pt(II) Intermolecular Olefin Hydroamination

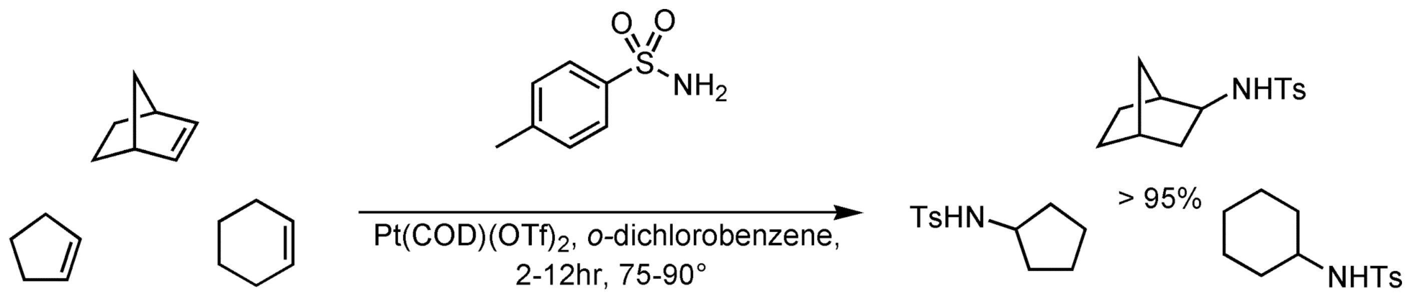


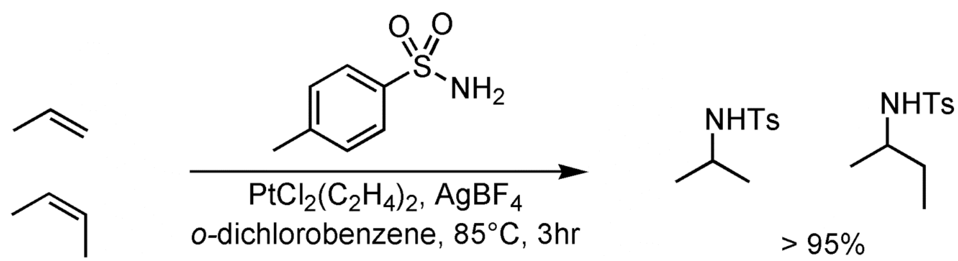
Widenhoefer et al. *Organometallics* **2004**, *23*, 1649.



Widenhoefer et al. *Org. Lett.* **2005**, *7*, 2635.

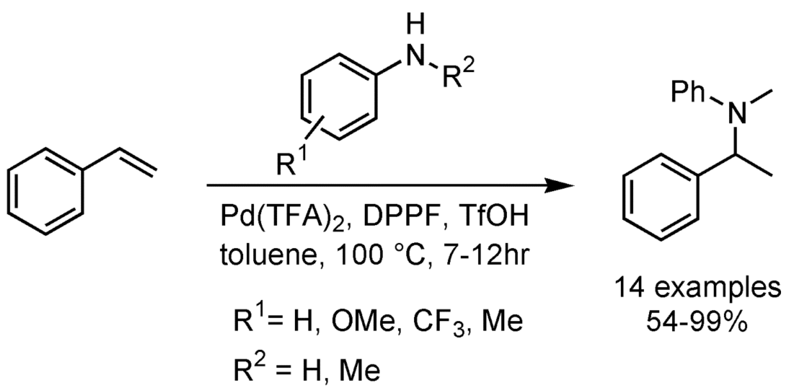
Tilley's Work with Pt Catalyzed Hydroamination



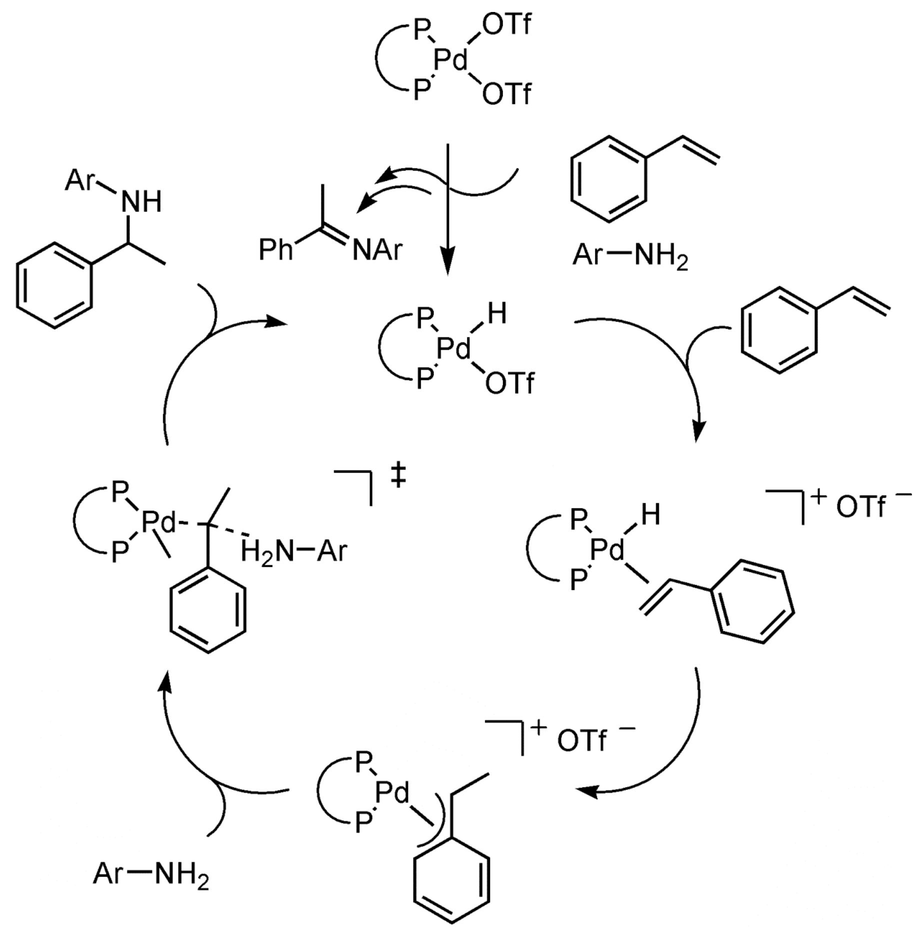


Tilley et al. *J. Am. Chem. Soc.* **2005**, *127*, 12642.

Hartwig's Hydroamination of Vinylarenes with Aniline

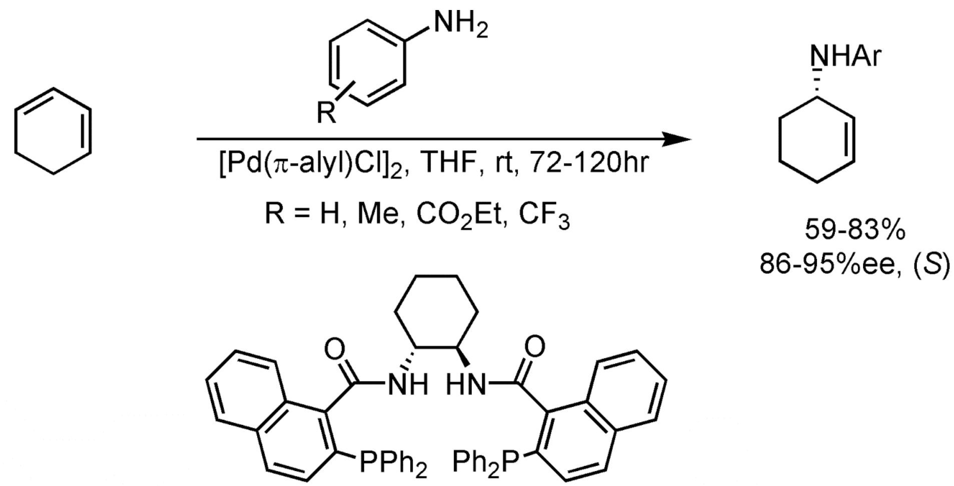


Hartwig et al. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

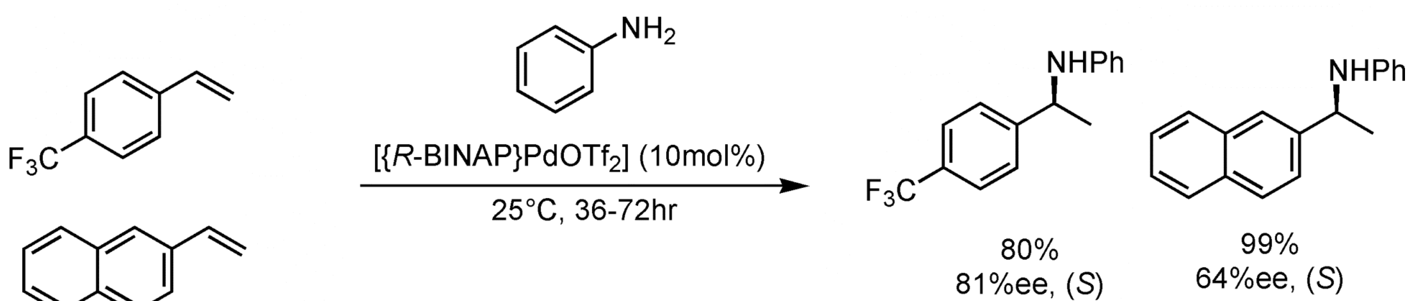


Hartwig et al. *J. Am. Chem. Soc.* **2002**, *124*, 1166.

Hartwig's Asymmetric Intermolecular Hydroaminations



Hartwig et al. *J. Am. Chem. Soc.* **2001**, *124*, 4366.



Hartwig et al. *J. Am. Chem. Soc.* **2000**, *123*, 9546.

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